

## PRELIMINARY NOTES

# Assessment of Drugs by Functional Imaging of Thallium-201 Distribution in the Dog

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**The effect of drugs on thallium-201 biodistribution in the body has been studied in dogs using a new functional imaging method. The calculation is based upon the comparison of the activities of the two scintigraphic images obtained after two successive injections of thallium-201 separated by an interval of at least 10 min, during which some drug of interest can be administered. This imaging technique was applied in control dogs (n = 6) and in animals treated with dipyridamole (n = 7) or grisorixin (n = 7). As expected, these two vasoactive drugs increased mainly the myocardial uptake, whereas smaller variations were noted in the other organs studied: liver, kidney, lungs, and skeletal muscles.**

**Thus this method should allow a rapid and reliable noninvasive assessment of cardiovascular drugs with thallium-201.**

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Thallium-201 has become a widely used radiotracer for myocardial imaging because of its physical and physiological properties (1-4). These are still not optimal, given the low-energy (x-ray) emission leading to a non-negligible attenuation in depth and the 73-hr half-life of Tl-201, which prevents the use of high injected activities; nevertheless, its biological behavior is very similar to that of potassium in the patient at rest, and its myocardial distribution is proportional to the local blood flow (5, 6). It is thus useful for the external detection of myocardial ischemia and necrosis. However, non-negligible extramyocardial uptake by organs such as the lungs, liver, spleen, kidneys, and muscles also occurs, and to an extent that depends, furthermore, on the physiological state of the recipient (7). No clinical interest has yet been found in these extracardiac uptakes, except in a recent paper where lung uptake was shown to be an indicator of cardiac insufficiency (8). The main problem in quantitating the regional uptake is the choice of a

region of reference, since uptake in any particular region varies from one subject to another and in the same subject from one examination to another.

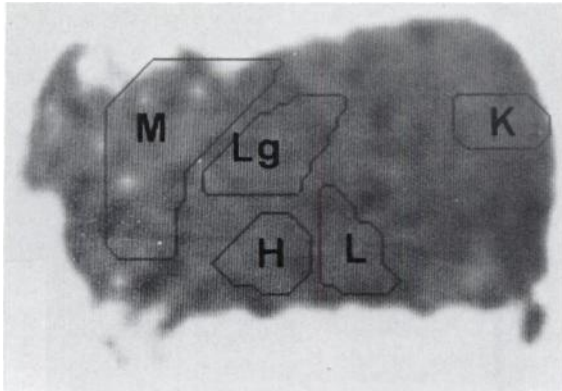
We introduce in this paper a new method, which enables us to assess—point by point, with each point being its own reference—the evolution of the regional uptake of thallium-201 between two situations: first, the basal state, and second, the state after pharmacological intervention. This is done by the injection of two half-doses of tracer separated by the injection of the drug under study. The point-by-point computer processing of the sequential scintigraphic frames stored during the study produces a functional image in which the regional differences in the thallium-201 uptake in the two situations are expressed. A well-known coronary dilator, dipyridamole, and a new one, the monocarboxylic ionophore grisorixin (9), were used in this study to evaluate the effectiveness of the method.

### MATERIAL AND METHODS

Twenty experiments were performed in mongrel dogs of either sex, weighing 10-20 kg and anesthetized with

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**FIG. 1.** Functional image obtained in control dog; no significant difference in contrast is observed between heart (H), liver (L), lungs (Lg), muscles (M), or kidneys (K).

sodium pentobarbital (30 mg/kg i.v.). All injections were performed intravenously through a cephalic vein. The controls received two injections of thallium-201 chloride (1 mCi/ml solution), with a 10-min interval between them. The treated dogs first received a half-dose of thallium-201, then a drug injection 10 min later, then again Tl-201 at half-dose, 3 min after a dipyridamole injection (0.5 mg/kg), or 5 min after grisorixin\* (100  $\mu$ g/kg). Grisorixin was administered in a water/ethanol mixture (70:30, v/v), 0.5 mg/ml. The mean total activity injected was about 1 mCi per animal.

The dogs were positioned under a large-field (40-cm) scintillation camera† equipped with a low-energy parallel-hole collimator. All images were left lateral. Pulse-height selection bracketed the 69–83 keV x-ray emission of the mercury daughter with a 25% window, and the 167-keV gamma emission with a 12.5% window. Starting from the first injection, sequential images of 30 sec each were stored in a computer for at least 20 min. The memory disc used a 64  $\times$  64 matrix.

The processing was done by dividing pixel by pixel the addition of the first five files following the second Tl-201 injection by the addition of the last five files preceding the drug injection. A pixel-by-pixel correction of the evolution of the activity during the ten minutes following the first injection was then performed; this permitted an estimate of the tail of the first injection, lying under the initial part of the second injection, to be subtracted out, leaving only the increase due to the second injection to be taken into account. The value of each pixel of the functional image was multiplied by 100 and corrected from the ratio of the activities of the two injected doses, calculated to include the whole body of the dog, so that the normal resulting value for each pixel was about 100 in the control group.

The pictures were then displayed in black and white on a TV screen. From regions of interest drawn by hand delineating areas for the heart, lungs, liver, kidneys, and skeletal muscle, the global effect of the drug under in-

vestigation upon their respective Tl-201 uptakes could be compared and quantitated. In practice, the display of the first image of the series, including the first pass of the tracer in the lungs, allowed easy drawing of the region of interest including this organ; heart, liver, and kidneys were delineated on the last image of the series, where they were always clearly seen. The muscular ROI was located in the anterior thoracic region between the lungs and head (Fig. 1).

## RESULTS

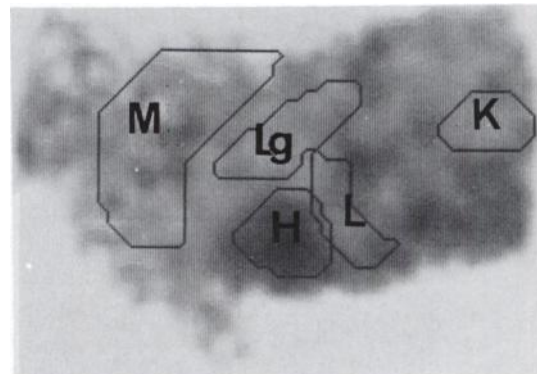
Figure 1 shows a functional image obtained in the basal state, with the regions of interest outlined for calculation of the relative uptake of thallium-201 between the two injections. The very similar values obtained, whatever the region of interest, are reflected by the low-noise, smooth aspect of the surface on the functional image.

By contrast, in a dog treated with dipyridamole (Fig. 2), the myocardium shows the highest relative post-treatment increase in uptake; the areas for the lungs and kidneys show relatively low values. When treated with grisorixin (Fig. 3), the same dog gives a similar but stronger myocardial picture, together with enhanced uptake in the skeletal muscles.

The complete results are presented in Table 1. In the basal conditions, all the calculated mean values are very near 100%, with a standard deviation that exceeds 3.1% only for muscle. However the mean  $\pm$  1 s.d. interval always includes 100%. With dipyridamole, the myocardium shows the highest increase, followed by the liver. With grisorixin, the highest value of the study is observed in the myocardium, but the Tl-201 uptake also increases in the skeletal muscles. With both treatments, the kidneys show a significant decrease.

## DISCUSSION

The values obtained in the basal state show that this technique can yield accurate results for the study of thallium-201 uptake in all the organs tested. This is



**FIG. 2.** Functional image in dog treated with dipyridamole (0.5 mg/kg), showing predominant cardiac effect (H).

achieved by using a very simple procedure for the processing, in which the intervention of the operator has very little effect on the final resulting picture. An alternative method for normalization with respect to the two injected doses of thallium-201 would have been to measure the syringes in a well counter just before and after each injection. However, this would require more manipulations and we had found in a preliminary study that the slightly nonlinear response of the camera to the activity led to a small but significant bias in the results. The present data in the basal state show that the technique gives results that are very close to optimal. Thus, it provides reproducible results that may easily be obtained in different laboratories and may then be compared.

One advantage of this method is that the possible redistribution of the thallium first injected has no effect on the final functional image, since after the first injection of Tl-201 the drug effect is assessed by taking into account only the absolute cell-by-cell increase in activity following the second injection, but not the absolute cell-by-cell total activity. This is done by comparing the activity observed just before the second injection with the activity observed two to three minutes after it. The time interval between these two measurements is that necessary for sufficient blood clearance of the tracer and significant organ uptake. Thus, the final result could be affected only by some rapid effect (unlikely and in fact never observed) that could induce a significant redistribution of the first dose of thallium during the 2- to 3-min distribution period of the second dose.

The myocardial uptakes observed with grisorixin are of the same order as those obtained in an experimental measurement of the true myocardial uptake of thallium-201 in the guinea pig (10). Even if this remains to be proven in the dog, it suggests that this technique could provide, atraumatically, results similar to those of a postmortem count of the dog's myocardium. This could be of great interest in the screening of new drugs or for rapidly and comparatively studying, in the same animal, the multiorgan effects of incompletely known drugs or

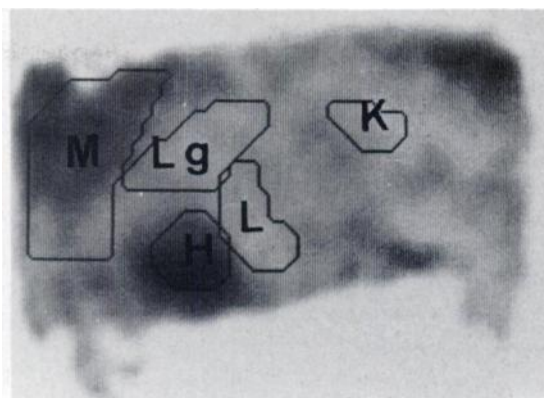


FIG. 3. Functional image in dog treated with grisorixin (100  $\mu\text{g}/\text{kg}$ ). Both heart and muscles exhibit an improvement in tracer uptake; concurrently, other organs (particularly liver) show decreased uptake.

of certain combinations. Since it is also a safe procedure, it could be used in man to study the effect of known drugs and to test individual reactions.

#### FOOTNOTES

\* Grisorixin was a gift from Dr. G. Jeminet, Laboratoire de Chimie Organique Biologique, Université Clermont II, France.

† General Electric 400T.

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**TABLE 1. NORMALIZED RATIO OF THE VARIATION IN ACTIVITY FOLLOWING TWO SUCCESSIVE INJECTIONS OF THALLIUM-201 IN PROJECTION OF DIFFERENT AREAS IN UNTREATED AND TREATED DOGS. RESULTS ARE EXPRESSED AS MEAN PERCENTAGE DEVIATION,  $\pm$  STANDARD DEVIATION OF THE EXPECTED NORMAL VALUE; THE LEVEL OF SIGNIFICANCE IS DETERMINED BY COMPARISON WITH THE CONTROLS USING STUDENT'S T-TEST FOR UNPAIRED VALUES.**

	Normal n = 6	Treated with dipyridamole n = 7	Treated with grisorixin n = 7
Myocardium	100.7 $\pm$ 3.1	129.0 $\pm$ 12.2 (P < 0.001)	139.7 $\pm$ 8.1 (P < 0.001)
Liver	100.0 $\pm$ 2.7	105.4 $\pm$ 7.0 (N.S.)	99.4 $\pm$ 6.1 (N.S.)
Kidneys	98.8 $\pm$ 2.4	89.0 $\pm$ 3.7 (P < 0.01)	86.0 $\pm$ 4.7 (P < 0.001)
Skeletal muscles	99.3 $\pm$ 4.3	93.4 $\pm$ 12.0 (N.S.)	112.1 $\pm$ 14.5 (P < 0.05)
Lungs	99.2 $\pm$ 1.7	90.1 $\pm$ 7.6 (P < 0.02)	90.9 $\pm$ 6.9 (P < 0.02)

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